Summary of the C-PORT Response to Comments of the Research Proposal Review Committee

on the

Scientific Merit of the Atlantic C-PORT Trial: Proposed Non-Primary Percutaneous Coronary Intervention (PCI)* Study Version 2.5 March 22, 2005

August 25, 2006

***Non-primary PCI includes elective angioplasty.**

Background

In Maryland, state health policy requires hospitals performing elective percutaneous coronary intervention (PCI) services, including elective angioplasty, to have cardiac surgery services on-site. This policy reflects clinical evidence from medical research, American College of Cardiology/American Heart Association guidelines, and the expertise and advice of cardiologists and cardiac surgeons. In 2003, the Maryland Health Care Commission appointed an Interventional Cardiology Subcommittee to provide advice on a number of policy issues regarding PCI services. The Subcommittee, which was chaired by David O. Williams, M.D., considered the appropriateness of a research project assessing the safety and efficacy of elective angioplasty in hospitals without on-site cardiac surgery backup. Based on the Subcommittee's recommendations, an updated Maryland State Health Plan was approved in 2004 that included policies permitting the Commission to consider applications for a waiver from the requirement for on-site cardiac surgery from hospitals interested in participating in a well-designed, peer reviewed study to determine the safety of elective PCI performed in hospitals without cardiac surgery on-site (SOS). As part of this policy, the Commission established a Research Proposal Review Committee to review and make recommendations on the design and implementation of any proposed research study seeking the participation of non-SOS hospitals in Maryland.

Composition of the Committee

The Research Proposal Review Committee is comprised of 24-members (Figure 1) representing the disciplines of cardiology, cardiac surgery, law, medicine, and bioethics. The committee is currently chaired by David P. Faxon, M.D., who is Vice Chair of the Department of Medicine at Brigham and Women's Hospital in Boston, Massachusetts.[1]

Committee Action

In January 2005, the Maryland Health Care Commission received a research proposal from the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) to conduct a study of the safety and outcomes of elective PCI performed in Maryland hospitals without on-site cardiac surgery. At the time of the submission, the C-PORT group was conducting similar research at non-SOS hospitals in several other states. Although the proposal, the Atlantic C-PORT Trial: Proposed Non-Primary Percutaneous Coronary Intervention (PCI) Study, refers to elective angioplasty, the study population is expected to include more patients with acute disease (e.g., unstable angina and non-ST-segment elevation myocardial infarction) and fewer stable patients for whom the procedure is truly elective. Hence, the term non-primary is used herein instead of elective.

[1] Thomas J. Ryan, M.D. served as Chairman of the Research Proposal Review Committee during 2005.

Figure 1
Maryland Health Care Commission
Research Proposal Review Committee

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The proposal was referred to the Research Proposal Review Committee for scientific review. The Committee was asked whether the trial, if appropriately designed and successfully executed, might provide a scientific basis for considering a change in state policy governing co-location of non-primary PCI and cardiac surgery services. In reviewing the proposed study, the Committee considered the following:

Study Protocol:

- What are the strengths and weaknesses of the following?
    1. Study Design
    2. Primary and Secondary Endpoints
    3. Definition of Terms
    4. Structure
        a. Clinical Coordinating Center
        b. Core Laboratories
        c. Study Coordinators

Sample Size and Statistical Considerations:

- What are the strengths and weaknesses of the statistical design?
- Does the study have a sample size that will produce meaningful results?

Source and Amount of Funding:

- What is the likelihood that funding would be available from a national organization to support the study?
- Is the amount of funding proposed from each participating hospital sufficient?
- What are the strengths and weaknesses of funding the study through an assessment on participating sites?

On April 19, 2005, the Committee met with the principal investigator, Thomas Aversano, M.D. of the Johns Hopkins Medical Institutions, Baltimore, Maryland, and members of the C-PORT group, representatives of health care agencies in other states where similar research is being conducted and other interested parties. Following this meeting and the receipt of written comments from individual Committee members, the Committee's findings and recommendations were communicated to Dr. Aversano and colleagues in a report dated August 16, 2005. The Committee offered specific comments and suggestions relative to a variety of procedural and analytical details addressed in the proposal. In addition, the Committee observed that the proposal lacked the scientific rigor to provide an evidence-based justification for the establishment by the Maryland Health Care Commission of a waiver program to allow non-SOS hospitals in the state to perform non-primary PCI. The Committee noted that:

- The selection of mortality as the sole primary endpoint is inadequate, i.e., it is necessary that there be no difference in mortality but major adverse cardiovascular events (MACE) must be similar to establish non-inferiority of safety, and quality, caliber, durability, and completeness of revascularization must be non-inferior to assure efficacy;

- No formal statistical analysis is proposed in the protocol; and

- There is no indication of how the study would be interpreted if mortality shows no difference (non-inferiority) but the secondary endpoints show greater MACE or one component of MACE, e.g., an increased number of target vessel revascularizations occurring in the non-SOS hospitals.

C-PORT Response and Resubmission

In March 2006, the C-PORT investigators submitted a revised proposal to the Commission, which included an updated Manual of Operations for the proposed study. These two documents address and incorporate the comments and suggestions made by the Research Proposal Review Committee in August 2005. In an accompanying commentary, the C-PORT group highlighted specific comments made by the Committee and their responses to those comments.

The following summarizes the issues of concern to the Committee that emerged from their review of the initial (2005) C-PORT proposal; these are shown in italics. The responses of the C-PORT investigators to each issue are presented in regular type, and are based largely on their commentary.

Study Design

Patient Population and Randomization

Research Proposal Review Committee Comments:

- *Unlike other clinical trials for evaluating cardiovascular treatments, the proposed study randomizes only patients who present to community hospitals to either a) remain in the community hospital and undergo PCI with SOS, or b) transfer to the tertiary hospital and undergo PCI with SOS. Part of what the proposal randomizes is location of procedure in terms of site selection.*
- *The study subjects, who self-select hospitals without SOS, may not be representative of the population of all likely non-primary PCI patients. A study using two-way randomization would randomize clinically eligible patients who go to hospitals with SOS or to hospitals without SOS.*
- *The study proposes the extension of non-primary PCI to hospitals without SOS as one model that may increase access to appropriate care and reduce morbidity and mortality among patients. Here it is important to distinguish between access to care versus convenience of care.*

C-PORT Response. The C-PORT investigators state that randomizing PCI-eligible patients who present to hospitals with on-site cardiac surgery to a hospital without on-site cardiac surgery either before or after diagnostic catheterization is neither realistic nor feasible. The "self-selection" process referred to by the Committee reflects the real world, particularly for patients who live at a substantial geographic or temporal distance from a tertiary care facility.

As part of the study design, PCI services will be available in participating non-SOS hospitals that currently do not offer these services. The investigators indicate that the study will increase access to care, thus reducing morbidity and mortality among patients with coronary artery disease (CAD) by: (1) sustaining life-saving and morbidity-reducing primary PCI programs that are difficult to sustain as stand-alone programs in terms of both finances and personnel; (2) improving access to PCI services in general, which may be life-saving; and, (3) expanding the "Centers of Excellence" approach to treating CAD, a disease of epidemic proportions. The distinction between access to care and convenience of care is not always clear – the latter may, for many reasons, influence the former in a variety of circumstances. If a hospital does not have adequate cardiology services because it can neither recruit nor retain competent cardiologists or other cardiology specialists, the available providers may not recognize the need for, or potential benefit of, transferring a patient for needed PCI services. Such a scenario creates a functional barrier to access. Data from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative and from the experience of Department of Veterans Affairs' hospitals with acute coronary syndrome and post-myocardial infarction patients demonstrate the benefit of reducing functional barriers to access for PCI services.

Stratification of Randomization

Research Proposal Review Committee Comments:

- *Non-primary PCI patients include patients with very different rates of potential complications and outcomes. Risk factors that may affect the primary or secondary outcomes should be comparable or balanced in randomization. The committee suggested that the investigators consider using stratification to address the potential for imbalance in the 3:1 randomization scheme.*

C-PORT Response. The C-PORT study Steering Committee and statisticians at the Maryland Medical Research Institute considered the Research Proposal Review Committee's suggestion of stratifying patient randomization. The pre-procedure stratification scheme most easily applied would assign patients to two clinical groups, those with acute coronary syndrome (ACS) and those without ACS. Based on several published registries, approximately 65% of patients will have some form of ACS and 35% will be non-ACS patients. Given this clinical distribution and a study population of 18,000 patients (~400 or more at each participating site), the risk of imbalance among clinical groups, or in terms of other risk factors in the two treatment arms is negligible and stratification is not necessary.

Protocol Deviations (Withdrawals and Crossovers)

Research Proposal Review Committee Comments:

- *Most trials do not proceed entirely in compliance with the study protocol. Patients who are randomized to remain at the hospital without SOS may switch to a*

hospital with SOS. Crossovers and protocol deviations can reduce the power of the clinical trial to detect a difference in outcomes between the two strategies.

- *The committee suggested that the study should collect data on eligible patients who withdraw from the study after catheterization.*
- *The study design should specify how the investigators will deal with protocol noncompliance and how they will assign the responsibility of handling crossovers.*
- *From the point of view of randomization and analysis, the protocol should also give some guidance on how the study would deal with the outcome (mortality of a patient who received PCI at the community hospital for one lesion, and was transferred to a tertiary center for the second lesion.*

C-PORT Response. Because patients are randomized to treatment immediately after catheterization and typically undergo PCI shortly thereafter, it is unlikely that a significant number of patients will withdraw from the study after catheterization and prior to PCI. However, if a patient withdraws from the study and declines additional follow-up, that request must be honored. As recommended by the Research Proposal Review Committee, data for all patients who withdraw in this way will be entered and retained in the study database to facilitate analysis of their clinical profiles.

The study is designed in such a way that crossovers should not occur. After catheterization and prior to randomization, the on-site investigator and catheterization laboratory staff must determine whether all lesions requiring PCI can undergo the procedure at the hospital without SOS. Indeed, when a hospital staff member calls the C-PORT Automated Telephone Response System to access the pre-randomization interrogation algorithm used to assign the patient to treatment, they are asked this question. If the answer is “no”, the patient is ineligible for the study and should not be randomized. If the answer is “yes”, the patient is randomized to the appropriate treatment group. This strategy will minimize the chance that one lesion will undergo PCI at one location and a second lesion will undergo PCI at the alternate location. In any event, analysis of the primary endpoints will be by intention-to-treat, with clear statements about the degree and nature of any crossovers or protocol violations.

Because the study continues for 9-months, the study investigators expect patients to remain in the same treatment group throughout the study period. The C-PORT investigators attribute this to several factors. First, patients are cared for by their local health care providers (i.e., their local physicians are their “study” physicians). Second, patients are likely to return to their local providers and to their community hospital for any required subsequent care. Third, patients may only have PCI at a non-SOS hospital that is part of the C-PORT project. Thus, patients initially randomized to PCI at the hospital with SOS must have PCI at that site; PCI at a hospital without SOS that is not part of this study would violate Maryland health care regulations.

The C-PORT investigators acknowledge that some of the expectations for the study may be modified as the ‘real world’ dictates. Thus, if a patient initially treated at one type of institution presents with an acute ST-segment elevation myocardial infarction (STEMI) at the alternate institution, then emergent removal to the presenting hospital catheterization

laboratory should occur without regard to initial treatment allocation. Similarly, if a patient presents to a hospital in another local (e.g., during travel) and requires revascularization, the patient and local physician may decide that revascularization at that hospital is in the patient's best interest. Finally, if a patient allocated to PCI at a hospital with SOS needs subsequent revascularization using a niche device (e.g., rotational atherectomy) not available at the hospital without SOS, the patient will have that revascularization at a hospital with SOS. Such crossover scenarios are likely to occur in the real world setting of offering PCI at non-SOS hospitals.

Primary Endpoints and Expected Event Rates

Research Proposal Review Committee Comments:

- *The committee suggested that, in a non-inferiority trial with the potential for low event rates, the investigators should address how the study will be defined if the mortality rates in the two groups are lower than expected. For example, the trial must collect a specific number of events, or the study is invalid or inconclusive. Assuming that mortality is not inferior, the investigators should also specify how a combination of the secondary endpoints will be interpreted and defined as statistically significant.*
- *PCI in the proposed study population is associated with a low incidence of mortality, which has been selected as the primary endpoint of the study. Even at 6 weeks, the event rate will be low (< 1.5 %) and this increases the number of patients who must be randomized to allow for an adequate number of endpoints to accumulate to permit reasonable statistical analyses. In a trial designed to evaluate endpoints other than death (such as MACE), the definition of these variables must be extremely clear.*
- *Further, they should define key terms, such as myocardial infarction as a complication of PCI.*

C-PORT Response. The definition of secondary endpoints has been revised in the Manual of Operations, version 3.0, 2006. For example, myocardial infarction (of various types) is defined in data element 420. The C-PORT study uses commonly accepted definitions that are comparable to definitions used in other studies to ensure that the outcome of the study is easily understood.

C-PORT investigators anticipate that the mortality rate at six weeks after index PCI will be near 1%, but acknowledge that this estimate is based on limited data. The investigators concurred with the Committee's concerns about primary endpoints by revising the proposal to include both mortality at 6-weeks post-procedure and the incidence, at 9-months post-procedure, of composite MACE (=death + myocardial infarction + target vessel revascularization).

The revised study design requires both primary endpoints to be non-inferior. To facilitate this evaluation, the expected 6-week mortality event rate has been reduced to 0.8% and the margin reduced to 0.4%. Similarly, the 9-month MACE rate was estimated to be 12% with a 1.8 % non-inferiority margin. If mortality is very low, indicating non-inferiority at 6-weeks, interpretation will hinge on the 9-month MACE data. Additional

detail about endpoints and their analysis and interpretation can be found in the Manual of Operations, Chapters 5 and 6, version 3.0, 2006.

The Manual of Operations (Chapter 9, version 3.0, 2006) incorporates data definitions that conform to the American College of Cardiology's National Cardiac Data Registry (NCDR) Cardiac Catheterization Module 3.04 Data Definitions.

Core Angiography Sample

Research Proposal Review Committee Comments:

• *The committee suggested that the investigators should justify the angiographic sampling of the proposed study population. Is a 7.5% sample sufficient to determine the caliber, completeness, durability, and overall quality of the PCI procedure?*

C-PORT Response. The C-PORT investigators agreed with the sense of the Research Proposal Review Committee's comment inferring that anything other than a 100% sample cannot be used to assess the "caliber, completeness, durability, and overall quality of the PCI procedure" for the study as a whole. The revised proposal calls for randomly selecting 1,500 cine angiography films (~40 films per site) that will be read in a core angiography laboratory. This constitutes approximately 8% of the total study population. After consulting with core angiography investigators, the C-PORT group determined that reading more films will neither sufficiently improve the accuracy nor enhance the value of the core lab reading results. The purpose of the core lab reading is to (1) determine whether the angiographic outcomes of PCI are the same at hospitals with and without SOS and (2) compare core lab readings of PCI procedure outcomes with those of local physicians. It is not feasible for the core lab to read films for the entire patient population because of cost constraints.

Study Follow-up Period

Research Proposal Review Committee Comments:

• *The committee also suggested increasing the length of follow-up to one year to look at longer-term outcomes, which tend to be related to age, heart failure, and other non-angiographic criteria.*

C-PORT Response. The Data Safety and Monitoring Board established for the proposed study suggested increasing the length of follow-up to 9-months. This has been incorporated into the revised proposal. The above section on Primary Endpoints and Expected Event Rates provides additional information germane to increasing the length of the follow-up period.

Patient Consent Issues

Research Proposal Review Committee Comments:

- *In a 3:1 randomization scheme, the investigator personally derives benefit from the study (this may be lessened in a 1:1 randomization). The committee suggested that the investigators consider the use of standardized videos, a consent monitor, or other techniques to address the conflict of interest concerns. The committee suggested that, if a participating site uses an external institutional review board, the IRB should include community representation.*
- *The population to be studied in this proposal includes patients who are clinically unstable as well as patients who may be asymptomatic or have chronic stable coronary artery disease. Accordingly, they will have varying risk/benefit ratios, which will require appropriate language in the informed consent. The latter should also address the potential for conflict of interest on the part of the physician as investigator and on the part of the participating institution.*

C-PORT Response. A 3:1 randomization scheme was chosen to allow an adequate volume of cases to remain at hospitals without SOS because many studies show a relationship between procedural volume and outcome. A 1:1 randomization scheme may bias results in favor of hospitals with SOS and, more importantly, could compromise patient outcomes at non-SOS hospitals. Although the 3:1 scheme was not chosen to improve the financial situation of non-SOS hospitals, the C-PORT Data Safety and Monitoring Board recommended inclusion of the following language in the consent form:

> "There are no extra hospital costs to you for participating in this study. However, if you participate in this study and need an angioplasty that is performed at this hospital, this hospital may benefit financially because the fees for doing the angioplasty will be billed and collected by this hospital rather than another hospital where you would otherwise be sent for your procedure."

Regarding the potential for conflicts of interest among physicians at participating hospitals, the C-PORT investigators note that, typically, the same physician (or a member of his or her group) might perform PCI at several hospitals, including both those with and those without SOS. Thus, there is no financial incentive for physicians related to their participation in the study. However, there may be circumstances where a conflict arises or is perceived (e.g., when another physician performs and bills for the procedure). For this reason, the following language will be included in the consent form:

> "There are no extra physician costs to you for participating in this study. If you participate in this study and need an angioplasty, the doctor who performs the angioplasty at this hospital may benefit financially because he will collect the professional fees rather than the physician at the hospital where you would be sent for the procedure."

The broad spectrum of patients with CAD represented in the C-PORT trial precludes accurate pre-catheterization risk stratification. Patients presenting with STEMI, and those with cardiogenic shock will not be included in this study. Precise expression of the risk of any individual patient's underlying disease process is difficult, particularly when the overall risk is quite low. Furthermore, the potential additional risk to the study subject is not the underlying disease risk, but rather, the potential risk of having PCI at a hospital without SOS. This information is captured in the consent form.

Structure

Research Proposal Review Committee Comments:

- *Despite inclusion criterion related to performing primary PCI 24/7, the study investigator has no control over guaranteeing that a hospital will keep staff for 24/7 coverage for primary angioplasty.*
- *The committee suggested that the investigators should describe in detail the responsibilities of the DCC in its interaction with the CCC. More detail regarding interaction with the other cores (EQOL Coordinating Center and Angiography Core Laboratory) would also be helpful in understanding that there are adequate personnel to support those functions.*
- *The committee suggested that the investigators provide greater detail regarding the capture of complete and reliable follow-up data for the 6 months after the PCI procedure.*
- *Some interventionalists will find it feasible to perform PCI procedures at the community hospital as well as the tertiary center. On the other hand, there will be interventionalists at the community hospital who have chosen not to participate in this trial, and the committee questioned whether this will affect recruitment into the study.*

C-PORT Response. The Manual of Operations has been modified (Chapters 8-12, version 3.0, 2006) to more fully address the capture of complete and reliable follow-up data. Similarly, Chapter 11 (Version 3.0, 2006) has been revised to provide additional details about the responsibilities of the Data Coordinating Center (DCC) and its interaction with the Clinical Coordinating Center (CCC).

In addition, the C-PORT group's experience conducting a randomized study of primary PCI outcomes and of creating and maintaining a registry of data from such studies has established precedents and protocols for successfully obtaining requisite follow-up information. For example, the initial informed consent allows participating site coordinators to obtain medical and cost data throughout the study period. Each participating site's formal agreement with a tertiary care center provides for obtaining documentation relative to patients enrolled in the study. Various other protocols have been used by C-PORT to ensure that follow-up data are collected in a timely manner and are complete.

The C-PORT investigators agreed with the Research Proposal Review Committee regarding the potential negative impact on recruitment if interventionalists at community

hospitals choose not to participate. However, experience to date suggests that interventionalists in community hospitals can be readily recruited to participate in studies such as this. The investigators note that the C-PORT primary PCI project, which was initiated several years ago, requires that there be no disparity of opinion regarding application of PCI at hospitals without SOS not only among interventionalists, but also among staff cardiologists and medical staff in general.

The C-PORT investigators acknowledge that they cannot guarantee that a hospital will provide PCI services 24/7, even though 24/7 access is a requirement for participation in the study. Under the C-PORT protocol, the study investigator can terminate the participation of hospitals not meeting the 24/7 requirement. In addition, 24/7 coverage is required for both primary and non-primary PCI patients, because the latter may occasionally require off-hours emergency PCI procedures (e.g., for ischemic or abrupt closure).

Sample Size

Research Proposal Review Committee Comments:

- *Committee members questioned the selection of the selection of the study's primary endpoint (6 week mortality), suggested that many more endpoints should be measured. In addition, the study does not consider the effect on overall quality of care.*
- *The study should seek to enroll a greater number of participants in order to provide a hedge against the expected loss of participants.*
- *Study participants will be drawn exclusively from the pool of patients visiting hospitals without SOS. Members of the committee questioned whether this pool of patients is representative of all Maryland patients. Patients seeking care initially at hospitals without SOS may have a different medical profile, or even convenience preferences, than Maryland patients generally.*
- *Committee members further suggested that the target power of 80% for the study may be inadequate.*

C-PORT Response. As noted in the section on Primary Endpoints and Expected Event Rates, the revised proposal calls for a 9-month assessment of MACE endpoints in addition to the original 6-week mortality endpoint.

Recent studies that followed PCI patients for 9-months post-procedure report retention rates of 100%. The C-PORT investigators anticipate that the retention rate for the proposed study, which employs a similar design, also will be at or near 100%. The rationale for this expectation is that patients involved in the study will identify their community hospital and local physician as their preferred health care facility and provider, respectively. By doing so, they will be less likely to view the hospital as a research facility and the staff as impersonal researchers.

As noted in the section on Patient Population and Randomization, the C-PORT investigators have given considerable thought to this issue, and revised the proposal accordingly.

The power of a study is critical to its success and its impact on clinical practice, and is determined in part by the number of subjects participating in the study. The revised Manual of Operations (Chapters 5 and 6, version 3.0, 2006) details the power estimates for the proposed study. Based on the revised study design, the power for the 6-week mortality endpoint is 0.83 and power for the 9-month MACE endpoint is 0.97. The overall study power is conservatively estimated as the product of these two values, i.e., approximately 0.8. The C-PORT investigators do not believe that it is possible to further increase the power of the study without making it prohibitively expensive and, thus, no longer feasible.

Funding

Research Proposal Review Committee Comments:

• *Committee members questioned whether the proposed level of funding will be adequate. The relatively low levels of available funding may be influencing unduly the study's budget. The estimated time (0.4 FTE) required for the principal investigator appears to be under-budgeted and, in addition, the various sub-studies and Johns Hopkins' coordinating center are likely under-funded at $2.7 million. Non-SOS hospitals with catheterization labs may be able to sustain the program at $30,000 per year. Nonetheless, the committee concluded that even under the assumptions of the study's author's, the proposed budget contains no margin for error. Finally, the budget is unable to accommodate any increases in sample size should increases be necessary. It was noted that three current cardiac interventional trials funded by the National Institutes of Health are budgeted at $24 million, $30.0 million, and $40.0 million, respectively. These studies involve no more than 1,000 to 2,000 patients.*

C-PORT Response. The C-PORT investigators reiterated their lack of success in attracting Federal (e.g., National Institutes of Health or Agency for Healthcare Research and Quality) or private foundation funding for their previous study that examined the safety and outcomes associated with performing primary PCI in non-SOS hospitals. They attribute the lack of funding, in part, to the controversy surrounding both the primary PCI study and the proposed non-primary PCI study, and note that the slow pace at which funding decisions are made confounds efforts such as these that might improve clinical practice. They also acknowledge that securing funding from pharmaceutical and medical device manufacturers can lead to a shift in research priorities as well as fostering real or perceived conflicts of interest.

The investigators project an annual cost of $52,000 for each participating hospital for the first two-years of the study. Each hospital is expected to provide this level of funding to support its Clinical Coordinating Center, data collection and management infrastructure, angiographic core laboratory and other study-related costs. Hospitals also will be responsible for personnel costs associated with data collection.